Serum amyloid A providing a link between maternal inflammation and placental dysfunction

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Introduction

The pro-inflammatory response during maternal inflammation (MI) is thought to be a cause of preterm birth and perinatal sequelae. In our previous studies, we have found that MI is associated with altered uterine and placental blood flow and increased clotting. Serum amyloid A (SAA) is an acute phase protein that increases in response to inflammation and circulates in the serum after complexing with high-density lipoproteins (HDL). High levels of serum SAA has also been found in correlation with preterm birth. Furthermore, recent studies have shown that SAA induces tissue factor and leads to thrombin generation in a dose-dependent manner.

Objectives

We sought to examine the overall changes in SAA levels in different maternal organs as well as the placenta during maternal systemic inflammation in order to further analyze the mechanistic link between MI and altered blood flow to the placenta.

Materials and Methods

A well-established mouse model of maternal systemic inflammation was employed using intraperitoneal (IP) injection of lipopolysaccharide (LPS) 25μg (n=4) or phosphate-buffered saline (PBS) (n=4) at embryonic day (E) 17. Maternal heart, kidneys, and placentas were harvested from the LPS and PBS groups 24 hours post-injection on E18. Western blots of placentas from both LPS and PBS groups were analyzed for SAA protein expression. The presence of monomer SAA and SAA/HDL complex were also analyzed in the maternal heart, kidney, and placenta, using westerns with both SDS-denatured and native PAGE. Standard statistics were employed.

Results

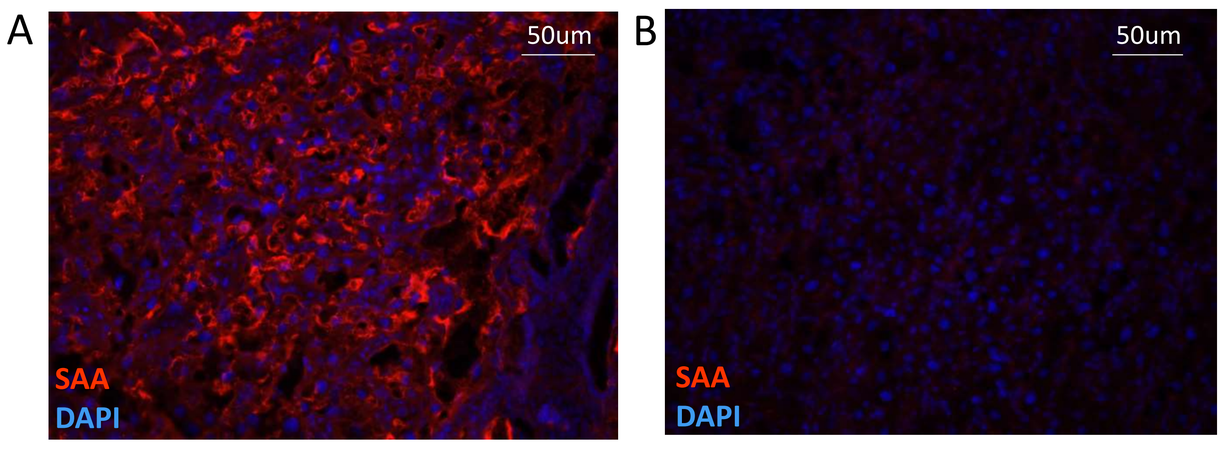

Figure 1. Increased SAA staining in the placental labyrinth of LPS compared with PBS dams There was an increase in SAA staining (red) in the placental labyrinth of E18-dams exposed to IP LPS (a) compared to the PBS (b) group 24 hours post-injection.

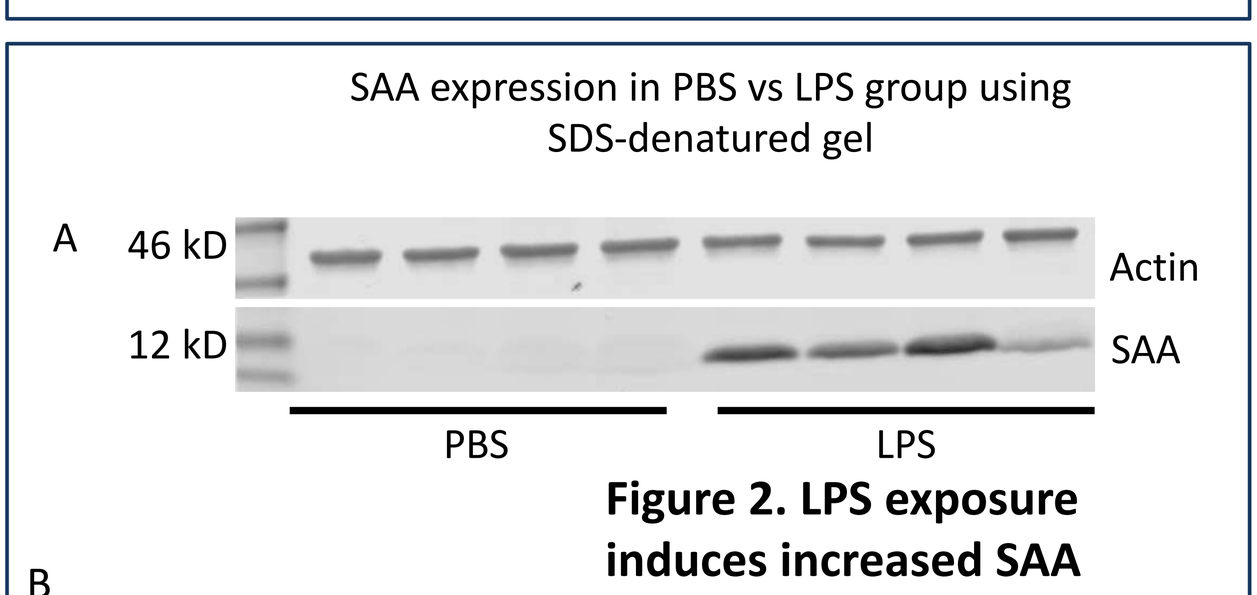

Figure 2. LPS exposure induces increased SAA expression in the placenta (A) SDS-denatured Western blots of placentas from PBS and LPS groups were performed to analyze SAA expression. Actin was used for normalization. (B) Student's T-test confirmed a 70-fold significant increase ($p<0.01$) in SAA expression when comparing LPS group with PBS group.

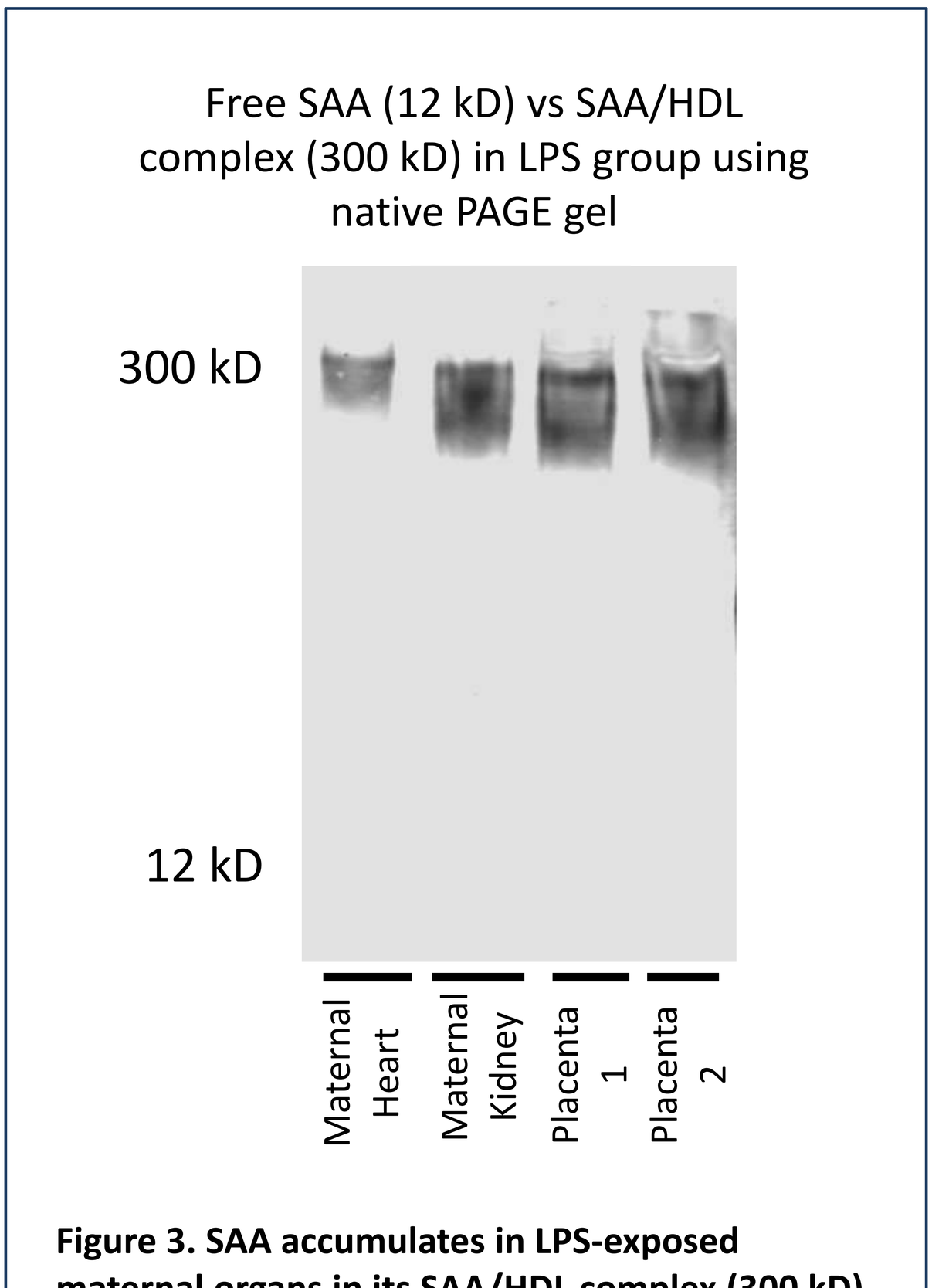

Figure 3. SAA accumulates in LPS-exposed maternal organs in its SAA/HDL complex (300 kD) form and not as free SAA (12 kD)
With native PAGE, no detectable free monomer SAA protein (12kD) was found in maternal heart, kidney, or placenta. Instead, all LPS-treated maternal organs and placentas only exhibited the accumulation of the SAA/HDL complex (300kD).

Conclusion

(i)SAA increases 70-fold in the placenta in response to LPS-induced MI.
(ii)Native SAA accumulates in its large (300kD) SAA/HDL complex form in the placenta and other maternal organs during inflammation.
(iii)These results suggest that SAA/HDL complex may have a direct role in placental function and homeostasis during maternal systemic inflammation. This study proposes a novel mechanistic explanation for the link between MI and altered blood flow to the placenta, and further research should discern the significance of SAA among other factors in this process.